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September 10, 1999

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm. 1061
Rockville, MD 20852

Re: Docket Number 99N-0193

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the Proposed Rule: Supplements and Other Changes to an Approved Application. In general, this proposed rule for revisions to 21 CFR 314.70 and other sections of 21 CFR clarifies some of FDA's expectations about changes to an approved NDA or ANDA. In that respect it is useful. However, we believe that the intent of the FDA Modernization Act was to identify a small number of major manufacturing changes that require prior approval but that most changes would require a less burdensome means of reporting than has been required in the past. However, other than the introduction of the category of "Changes Being Effected in 30 days" and the addition of a few definitions, it appears that little has changed from the current 21 CFR 314.70.

Specific comments are attached with a reference to the section of the rule. Some of these comments also apply to the proposed guideline on reclassification of requirements, however specifics on the proposed guideline have been addressed in a previous letter.

If there are any questions or if I can be of further assistance, feel free to call on me. My phone number is 513-622-3914 and my E-mail address is welles.hl@pg.com.

Sincerely,

Harry L. Welles, Ph.D.
Principal Scientist
Regulatory Affairs

99N-0193

C17

Section	Change
314.70 (a)(6)	Change "list all of all changes" to "a brief summary of major changes". In an active submission, a complete listing of all minor changes in the cover letter to the Annual Report is not likely to be useful. Also, there is no regulatory requirement that an Annual Report have a cover letter.
314.70 (b)(2)(iii)	Change "may affect product sterility assurance" to "is likely to affect product sterility assurance". Many factors may influence sterility, but this stringent reporting requirement should be reserved for factors that are have significant potential to cause a change.
314.70 (b)(2)(iv) and (b)(2)(iv)	Change "may affect the impurity profile of the drug product" to "are likely to affect the impurity profile of the drug product." Many factors could affect the impurity profile, but this stringent reporting requirement should be reserved for factors that are likely to produce a change.
314.70 (c)(1)	Delete the requirement to provide 12 copies of the final printed labeling with a CBE labeling supplement. Although the specified changes may be submitted in a CBE, at times they may not be implemented until some time after the submission. To print final labeling specifically for the CBE is unnecessarily expensive and complicates the normal labeling printing process. An alternative would be to submit a typed copy of the labeling, and submit the final printed labeling in the Annual Report.
314.70 (d)(2)(i)	Change to read "Any change made to comply with an official compendium." Section 501 (b) of the FD&C Act requires manufacturers to comply with the official compendia or describe in the label of the product how it does not comply. Further, if FDA finds any compendial requirement to be insufficient, it is required to resolve the difference between FDA and the compendium. If that is not possible, FDA is directed to "promulgate regulations prescribing appropriate tests ..." The applicant should not be placed in the middle of interactions between the compendium and FDA. Also, given the wording in the Act, FDA should enact appropriate regulations before forcing an applicant to deviate from the compendial requirements. It is understood that the NDA or ANDA may have some additional requirements that are not listed in the compendium, such as additional impurities specifications for an API, but this section does not appear to address this situation. In the absence of regulations identifying specific test requirements, any change made to comply with an official compendium should be an annual report change.
314.70 (b)(3)(vii)	It is unclear what value a reference list of SOPs provides to the Division reviewer. This is a GMP issue and should be deleted from the proposed rule.

Comments – Proposed Rule: Supplements and other Changes to an Approved Application
Docket Number: 99N-0193
Procter & Gamble Pharmaceuticals

Section	Change
314.70 (d)(3)(iii)	Delete "a cross-reference to relevant validation protocols and/or SOPs". Validation protocols and SOPs are GMP issues, and should not be registration requirements.

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